

SN 09/512,962

Docket No. S-91,732

In Response to Office Action dated May 20, 2003

IN THE CLAIMS:

1-9 (Cancelled).

10. (Currently Amended) A method for improving an electron density map of an experimental crystal structure, comprising the steps of:

a-(a) forming a model electron density map from known crystallographic information of [a] an exemplary model crystal structure;

b-(b) forming model histograms of model electron densities in identified protein and solvent regions of the model electron density map;

c-(c) fitting a model probability distribution function defined by

$$p(\rho_r) = \sum_k w_k \exp \left\{ -\frac{(\rho - c_k)^2}{2\sigma_k^2} \right\}$$

to the model histograms, where k is separately indexed over the protein and solvent regions of the model map. $p(\rho_r)$ is a probability of an electron density at a point, w_k is a normalization factor, ρ is electron density, c_k is a mean value of ρ , and σ_k is a variance of ρ , where the fitting determines the coefficients w_k , c_k , and σ_k ;

d-(d) determining a set of experimental structure factors from x-ray diffraction data for the experimental crystal structure and forming an experimental electron density map;

e-(e) forming separate experimental histograms of experimental electron densities over protein and solvent regions of the model electron density map;

f-(f) fitting an experimental probability distribution function defined by

$$p(\rho_r) = \sum_k w_k \exp \left\{ -\frac{(\rho - \beta c_k)^2}{2(\beta \sigma_k^2 + \sigma_{exp}^2)} \right\}$$

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to separate protein and solvent regions of the experimental histograms, where β is an expectation that an experimental value of ρ is less than a true value and σ_{map} is a variance, where the fitting determines the coefficients β and σ_{map} ;

~~g.(g)~~ determine from the experimental probability distribution function the overall experimental log-likelihood of the electron density in the protein and solvent regions of the experimental map from the experimental probability distribution function

$$LL(\rho(\mathbf{x}, \{\mathbf{F}_h\})) = \ln [p(\rho(\mathbf{x})|PROT) p_{PROT}(\mathbf{x}) + p(\rho(\mathbf{x})|SOLV) p_{SOLV}(\mathbf{x})]$$

where $p_{PROT}(\mathbf{x})$ is the probability that \mathbf{x} is in the protein region and $p(\rho(\mathbf{x})|PROT)$ is the conditional probability for $\rho(\mathbf{x})$ given that \mathbf{x} is in the protein region, and $p_{SOLV}(\mathbf{x})$ and $p(\rho(\mathbf{x})|SOLV)$ are the corresponding quantities for the solvent region;

~~h.(h)~~ determine how the experimental log-likelihood of the electron density of the protein and solvent regions of the structure factor experimental electron density map would change as each experimental changes to output a revised log-likelihood of any value of each experimental structure factor; [and]

~~i.(i)~~ forming from the revised log-likelihood of experimental structure factor values a new set of structure factors and returning the new set of structure factors to step (f) to iterate the process until changes to a new set of structure factors are below a predetermined value; and

(i) forming a revised experimental electron density map from the revised structure factors.

11. (Currently Amended) ~~A-The~~ method according to Claim 10, wherein step ~~a.~~ (a) further includes a step of selecting the model crystal structure to be similar in size, data resolution, and atomic displacement factors to the experimental crystal structure.

12. (Currently Amended) ~~A-The~~ method according to Claim 10, wherein step ~~b.~~ (b) further includes a step of identifying protein and solvent regions by designating all points within a selected distance of an atom as "protein" and all other points as as "solvent."

13. (Currently Amended) ~~A-The~~ method according to Claim 11, wherein step ~~b.~~ (b) further includes a step of identifying protein and solvent regions by designating all

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points within a selected distance of an atom as "protein" and all other points at as "solvent."

14. (Currently Amended) ~~A~~The method according to Claim 10, wherein step ~~h~~ (h) includes steps of forming a Taylor's series expansion of the log-likelihood of the experimental electron density map and evaluating terms of the Taylor's series expansion using a Fast Fourier Transform.